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L7	layers	3492216	L7
L6	L5 with l4	40883	L6
L5	multipl$ or alterna$	2836864	L5
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L3	6730349.pn.	2	L3
L2	6607598.pn.	3	L2
L1	6368658.pn.	2	L1

END OF SEARCH HISTORY

pattern is preserved in the coated device.

Summary of Invention Paragraph:
[0022] The coated stents may thereafter be subjected to a postcure sterilization process which includes an inert gas plasma treatment, and then exposure to gamma radiation, electron beam, ethylene oxide (ETO) or steam sterilization may also be employed.

Summary of Invention Paragraph:
[0023] In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to about 20-50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to about 100-450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

Summary of Invention Paragraph:
[0024] After the argon plasma pretreatment, the coated and cured stents are subjected to gamma radiation sterilization nominally at 2.5-3.5 Mrad. The stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status. It has been found that constrained stents subjected to gamma sterilization without utilizing the argon plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

Summary of Invention Paragraph:
[0025] The elastomeric material that forms a major constituent of the stent coating should possess certain properties. It is preferably a suitable hydrophobic biostable elastomeric material which does not degrade and which minimizes tissue rejection and tissue inflammation and one which will undergo encapsulation by tissue adjacent to the stent implantation site. Polymers suitable for such coatings include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes (including polycarbonate urethanes), thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, EPDM rubbers and polyamide elastomers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention.

Summary of Invention Paragraph:
[0027] The preferred materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy.RTM. and Phynox.RTM.. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Pat. Nos. 4,655,771 and 4,954,126 to Wallsten and 5,061,275 to Wallsten et al. To the extent additional information contained in the above-referenced patents is necessary for an understanding of the present invention, they are deemed incorporated by reference herein.

Summary of Invention Paragraph:
[0028] Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

Brief Description of Drawings Paragraph:
[0041] FIGS. 8-11 are photomicrographs of coated stent fragments for the coatings of FIG. 7 having a corresponding average particle size of 4 microns, 17 microns, 22 microns and 30 microns, respectively.

Detail Description Paragraph:
[0042] According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in FIG. 1. The coating solutions or suspensions are prepared at 10 as will be described later. The desired amount of crosslinking agent is added to the suspension/solution as at 12 and material is then agitated or stirred to produce a homogenous coating composition at 14 which is thereafter transferred to an application container or device which may be a container for spray painting at 16. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

Detail Description Paragraph:
[0047] The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, typically a paint jar attached to an air brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0-160 psi). Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15-25 psi and the nozzle condition checked by depressing the trigger.

Detail Description Paragraph:
[0048] Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

Detail Description Paragraph:
[0049] With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2-4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, for a coating level of 3-4 mg of heparin per cm.sup.2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

Detail Description Paragraph:
[0050] The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30-50 rpm and with a spray nozzle flow rate in the range of 4-10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Detail Description Paragraph:
[0051] Several applied layers make up what is called the tie layer as at 18 and thereafter additional upper layers, which may be of a different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, are applied as the top layer as at 20. The application of the top layer follows the same coating procedure as the tie layer with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by modifying the speed of rotation of the stent and the spraying conditions. Generally, the total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

Detail Description Paragraph:
[0052] As shown at 22 in FIG. 1, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50.degree. C.) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90.degree. C. or higher for approximately 16 hours. The temperature may be raised to as high as 150.degree. C. for dexamethasone containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers, and biologically active species.

Detail Description Paragraph:
[0053] Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at 24 is first applied to the coated, cured stent.

Detail Description Paragraph:
[0054] The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, Calif.). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 mHz and from 0-500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

Detail Description Paragraph:
[0055] In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20-50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to 100-450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

Detail Description Paragraph:
[0056] After this, as shown at 26, the stents are exposed to gamma sterilization at 2.5-3.5 Mrad. The radiation may be carried out with the stent in either the

radially non-constrained status--or in the radially constrained status.

Detail Description Paragraph:
[0058] Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subcute thrombosis.

Detail Description Paragraph:
[0061] In addition, as shown in the photomicrographs of FIGS. 8-11, as the average particle size increases, the morphology of the coating surface also changes. Coatings containing larger particles (FIGS. 9-11) have very rough and irregular surface characteristics. These surface irregularities may be more thrombogenic or exhibit an increased tendency to cause embolization when the corresponding stent is implanted in a blood vessel.

Detail Description Paragraph:
[0063] What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be modified to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and anti-thrombotic drugs in the topcoat layer. In this manner, the anti-thrombotic drugs, for example, heparin, will elute first followed by antiproliferation drugs, e.g. dexamethasone, to better enable safe encapsulation of the implanted stent.

Detail Description Paragraph:
[0065] For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37.degree. C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

Detail Description Paragraph:
[0067] It will be appreciated that the mechanism of incorporation of the biologically active species into a thin surface coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Detail Description Paragraph:
[0069] Whereas the above examples depict-coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to

an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Detail Description Paragraph:
[0070] Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

Previous Doc Next Doc Go to Doc#

L11: Entry 34 of 75 File: PGPB May 9, 2002

DOCUMENT-IDENTIFIER: US 20020054900 A1
TITLE: Polymeric coatings for controlled delivery of active agents

Abstract Paragraph:
Implantable medical device having a structure adapted for introduction into a patient wherein the structure is composed of a base material positioned over the structure. The implantable medical device further includes at least one composite layer of a bioactive agent and a polymer material and at least a barrier layer positioned over the composite layer and being of thickness adequate to provide a controlled release of the bioactive agent. The barrier layer being applied by a low energy plasma polymerization process which includes placing the device with the at least one composite layer in a plasma chamber and introducing at least one monomer gas.

Summary of Invention Paragraph:
[0002] The present invention relates to methods and medical devices for the controlled, localized delivery of bioactive agents within a body.

Summary of Invention Paragraph:
[0003] The systemic administration of drug agents, such as by intravenous means, treats the body as a whole even though the disease to be treated may be localized. Thus, it has become common to treat a variety of medical conditions by introducing an implantable medical device partly or completely into a body cavity such as the esophagus, trachea, colon, biliary tract, urinary tract, vascular system or other location within a human or veterinary patient. For example, many treatments of the vascular system entail the introduction of a device such as a stent, catheter, balloon, guide wire, cannula or the like. One of the potential drawbacks to conventional drug delivery techniques with the use of these devices being introduced into and manipulated through the vascular system, is that blood vessel walls can be disturbed or injured. Clot formation or thrombosis often results at the injured site, causing stenosis (closure) of the blood vessel.

Summary of Invention Paragraph:
[0005] Many medical devices and therapeutic methods are known for the treatment of atherosclerotic disease. One particular therapy for certain atherosclerotic lesions is percutaneous transluminal coronary angioplasty (PTCA). Another therapy for certain atherosclerotic lesions is percutaneous transluminal angioplasty (PTA). During PTA, a deflated balloon-tipped catheter is inserted in a patient's artery. The tip of the catheter is advanced to the site of atherosclerotic plaque. Inflation of the balloon "cracks" the atherosclerotic plaque and expands the vessel, thereby relieving the stenosis, at least in part.

Summary of Invention Paragraph:
[0007] A device such as an intravascular stent including stent grafts and covered stents can be a useful adjunct to PTA, particularly in the case of either acute or threatened closure after angioplasty. The stent is placed in the dilated segment of the artery to mechanically prevent abrupt closure and restenosis. Unfortunately, even when the implantation of the stent is accompanied by aggressive and precise antiplatelet and anticoagulation therapy (typically by systemic administration), the incident of thrombotic vessel closure or other thrombotic complication remains

significant, and the prevention of restenosis is not as successful as desired. Furthermore, an undesirable side effect of the systemic antiplatelet and anticoagulation therapy is an increased incidence of bleeding complications, most often at the percutaneous entry site.

Summary of Invention Paragraph:
[0008] Other conditions and diseases are also treatable with stents, catheters, cannulae and other devices inserted into the esophagus, trachea, colon, biliary tract, urinary tract and other locations in the body, or with orthopedic devices, implants, or replacements, for example. One of the drawbacks of conventional means of drug delivery using such devices is the difficulty in effectively delivering the bioactive agent over a short term (that is, the initial hours and days after insertion of the device) as well as over a long term (the weeks and months after insertion of the device). Another difficulty with the conventional use of stents for drug delivery purposes is providing precise control over the delivery rate of the desired bioactive agents, drug agents or other bioactive material. The term "bioactive agent" is used herein to mean any agent such as a pharmaceutical agent or drug or other material that has a therapeutic effect.

Summary of Invention Paragraph:
[0011] The foregoing problems are solved and a technical advance is achieved in an illustrative vascular stent or other implantable medical device that provides a controlled release of at least one bioactive agent into the vascular or other system, or other location in the body, into which the stent or medical device is positioned. In one aspect, the present invention provides an implantable medical device having a structure adapted for introduction into a patient, e.g., a stent, coil, catheter, etc. The implantable medical device of the invention comprises at least one composite layer of a bioactive agent and a polymer material and at least one barrier layer positioned over the composite layer or layers. The barrier layer has a thickness adequate to provide a controlled release of the bioactive material. The barrier layer is applied to the medical device by a low energy plasma polymerization process which comprises placing the composite covered medical device in a plasma chamber and introducing at least one monomer gas into the chamber to form at least one barrier layer. In another embodiment of the invention, the barrier layer comprises at least one bioactive agent.

Summary of Invention Paragraph:
[0012] In another aspect, the present invention includes a method for the localized delivery of a bioactive agent to a target location within the body. The method includes the first steps of providing a medical device having a structure adapted for introduction into a patient wherein the structure is composed of a base material, at least one composite layer of a bioactive agent and a polymer material applied to the base material. At least one barrier layer is positioned over the composite layer and applied to the composite layer by a low energy plasma polymerization process. The barrier layer has a thickness adequate to provide a controlled release of the bioactive material. The plasma polymerization process includes the steps of placing the composite covered device in a plasma chamber and introducing at least one monomer gas into the plasma chamber to form at least one barrier layer on the outer surface of the composite covered device. The method for localized delivery of a bioactive material includes a second step of delivering the implantable medical device to the target location.

Brief Description of Drawings Paragraph:
[0014] FIG. 2 shows side and end views of a stent used in an embodiment of the present invention;

Detail Description Paragraph:
[0017] The present invention provides implantable medical devices and methods for the controlled, localized delivery of a bioactive agent to target locations within a body. The term "controlled localized delivery" as used herein is defined as a

characteristic release rate of the bioactive agent over a desired period of time at a fixed location. The implantable medical devices of the present invention may have a simple construction, provide a minimal cross-sectional profile, and allow for easy and reproducible loading of active agents, drug agents and bioactive material.

Detail Description Paragraph:
[0018] With reference to FIG. 1, an implantable medical device 1 in accordance with the present invention is shown and includes a structure 2 adapted for introduction into a patient. The term "adapted" is used herein to mean that the structure 2 is shaped and sized for such introduction. For clarity, only a portion of structure 2 is shown in FIG. 1.

Detail Description Paragraph:
[0019] By way of example, structure 2 is configured as a stent particularly adapted for insertion into the vascular system of the patient. As known in the art, stents are tubular support structures that are implanted in coronary and peripheral blood vessels or arteries or other non-vascular lumens, blood vessels or other tubular body lumens. The present invention can thus be used for the dual purpose of localized drug delivery and stent placement, for example. The stent structure may also be used in non-vascular systems and sites such as the esophagus, trachea, colon, biliary ducts, urethra, and ureters, among others. A stent 210 used with the present invention is of any suitable design and is configured in mesh design as shown in FIG. 2.

Detail Description Paragraph:
[0020] Referring back to FIG. 1, structure 2 is alternatively configured as any conventional vascular or other medical device, and includes any of a variety of conventional stent or other adjuncts, such as helically wound strands, perforated cylinders or the like. Accordingly, the structure 2 is configured as at least one, or any portion of, a medical device that is adapted for insertion into the body. Examples of such medical devices include catheters, guide wires, balloons, filters (e.g., vena cava filters), stents, stent grafts, vascular grafts, intraluminal paving systems, implants and other devices used in connection with drug-loaded polymer coatings. Such devices are implanted or otherwise utilized in body lumens and organs such as the coronary vasculature, esophagus, trachea, colon, biliary tract, urinary tract, prostate, brain, and the like. Examples of suitable vascular grafts are described in U.S. Pat. Nos. 5,509,931, 5,527,353, and 5,556,426. Vena cava filters such as those described in WO 96/12448 and WO 96/17634 may also be used in the present invention. All of foregoing documents identified by number are incorporated herein in their entireties.

Detail Description Paragraph:
[0021] The grafts, including stent grafts, that are provided with a bioactive agent-polymer composite layer in accordance with the present invention include synthetic vascular grafts that are used for replacement of blood vessels in part or in whole. A typical vascular graft is a synthetic tube with each end thereof sutured to the remaining ends of a blood vessel from which a diseased or otherwise damaged portion has been removed. In a typical stent graft, each end of the synthetic tube portion includes a stent that is affixed to each of the remaining ends of a blood vessel from which a diseased or otherwise damaged portion has been removed. Alternatively in a stent graft, the replacement vessel may be a segment of a vessel removed from another location in the patient, such as a portion of a femoral artery or the like. In the case of a synthetic graft, the graft is typically tubular and may be, e.g., of a woven, knit or velour construction. Preferred base materials for the grafts and covering material for the stent grafts include polyethylene terephthalate and polytetrafluoroethylene. The vascular grafts may be reinforced with, for example, helices, rings, etc. in order to provide uniform strength over the entire surface of the graft tubing. The materials with which such grafts are constructed are biologically compatible materials including,

but not limited to, thermoplastic materials such as polyester, polytetrafluoroethylene (PTFE), silicone and polyurethanes. The preferred materials include polyester fibers and PTFE.

Detail Description Paragraph:
[0024] A variety of conventional materials may be employed as the base material 3. For example, the base material 3 may be either elastic or inelastic. The base material 3 may be either biodegradable or nonbiodegradable. Moreover, some biologic agents have sufficient strength to serve as the base material 3 of structure 2, even if not especially useful in the exemplary coronary stent.

Detail Description Paragraph:
[0025] Accordingly, the base material 3 may be formed of stainless steel, tantalum, titanium, nitinol, gold, platinum, inconel, iridium, silver, tungsten, or another biocompatible metal, or alloys of any of these; carbon or carbon fiber; cellulose acetate, cellulose nitrate; silicone, polyethylene terephthalate, polyurethane, polyamide, polyester, polyorthoester, polyanhydride, polyether sulfone, polycarbonate, polypropylene, high molecular weight polyethylene, polytetrafluoroethylene, or another biocompatible polymeric material, or mixtures or copolymers of these; polylactic acid, polyglycolic acid or copolymers thereof, a polyanhydride, polycaprolactone, polyhydroxybutyrate valerate or another biodegradable polymer, or mixtures or copolymers of these; a protein, an extracellular matrix component, collagen, fibrin or another biologic agent; or a suitable mixture of any of these. Stainless steel and nitinol are particularly useful as base materials when the structure 2 is configured as a vascular stent.

Detail Description Paragraph:
[0026] The implantable medical device 1 of the present invention also includes at least one layer 5 formed by a composite of at least one bioactive agent and a biocompatible polymeric or copolymeric material. When multiple polymer-bioactive agent composite layers are used, the layers may contain the same or different bioactive agents and/or the same or different polymers. The combination of bioactive agent and polymer serves as a monolithic matrix depot of the bioactive agent. This depot contributes partially to providing control over the release rate of the bioactive agent from the medical device.

Detail Description Paragraph:
[0032] The biocompatible polymeric material used to form the bioactive agent-polymer composite layer(s)may include any polymeric material capable of forming a solidified composite layer in the presence of the bioactive material. The polymeric material of the present invention is hydrophilic or hydrophobic, and is, for example, polycarboxylic acids, cellulosic polymers, including cellulose acetate and cellulose nitrate, gelatin, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyanhydrides including maleic anhydride polymers, polyamides, polyvinyl alcohols, polyolefins, copolymers of vinyl monomers such as EVA, polyvinyl ethers, polyvinyl aromatics, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters including polyethylene terephthalate, polyacrylamides, polyethers, polyether sulfone, polycarbonate, polyalkylenes including polypropylene, polyethylene and high molecular weight polyethylene, halogenated polyalkylenes including polytetrafluoroethylene, polyurethanes, polyorthoesters, proteins, polypeptides, silicones, siloxane polymers, polylactic acid, polyglycolic acid, polycaprolactone, polyhydroxybutyrate valerate and blends and copolymers thereof as well as other biodegradable, bioabsorbable and biostable polymers and copolymers. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL.RTM., etc.) and acrylic latex dispersions are also within the scope of the present invention. The polymer may be a protein polymer, fibrin, collagen and derivatives thereof, polysaccharides such as celluloses, starches, dextrans, alginates and derivatives of these polysaccharides, an extracellular matrix component, hyaluronic acid, or another biologic agent or a suitable mixture of any of these, for example. Composite layer

5 can include of a single polymer or copolymer. It may also include copolymers or physical blends of any of the materials indicated above. In one embodiment of the invention, the preferred polymer is polyacrylic acid, available as HYDROPLUS.RTM. (Boston Scientific Corporation, Natick, Mass.), and described in U.S. Pat. No. 5,091,205, the disclosure of which is hereby incorporated herein by reference. U.S. Pat. No. 5,091,205 describes medical devices coated with one or more polyisocyanates such that the devices become instantly lubricious when exposed to body fluids. In a most preferred embodiment of the invention, the polymer is a polyurethane and derivatives thereof.

Detail Description Paragraph:
[0033] The use of the bioactive agent-polymer composite layer 5 in the present invention has the added advantage in that this layer or multilayers allow for enhanced adhesion of the mixture to the base material 3 as opposed to the prior art methods of first applying a polymer followed by a drug coating. The bioactive agent-polymer composite layer 5 also provides for an effective way of adjusting the amount of the bioactive agent placed on the base material 3. This is accomplished by adjusting the bioactive agent/polymer ratio and/or thickness of the bioactive agent-polymer composite layer. Also, composite layer 5 provides a co-compliant surface for a subsequent barrier layer and aids in maintaining the mechanical integrity of the barrier layer during the expansion of the medical device. The bioactive agent-polymer composite also has the added benefit of providing a blood compatible surface to the medical device. Thus, the biocompatible polymer material acts as an intermediary between the vascular walls or the blood stream and the implantable medical device 1.

Detail Description Paragraph:
[0035] Still with reference to FIG. 1, implantable medical device 1 of the present invention also includes at least one barrier layer 20 positioned over the bioactive agent-polymer composite layer(s) 5. One purpose of this barrier layer or layers is to provide further controlled release of the bioactive material when device 1 is positioned in the vascular system or other body lumen of a patient. The thickness of the barrier layer 6 is chosen so as to provide such control. Also, the barrier layer 20 protects the drug from the routine handling process and physiologic milieu until the drug reaches the target site. In an alternative embodiment of the invention, the barrier layer(s) may contain an additional bioactive agent which may be the same or different from the bioactive agent of the bioactive agent-polymer composite layer(s).

Detail Description Paragraph:
[0036] The barrier layer 20 is a polymer or copolymer layer deposited on the outer surface of the bioactive agent-polymer composite layer 5 by a vapor deposition process or a low energy plasma polymerization process. Low-energy plasma polymerization is performed by exposing the composite coated implantable medical device to a monomer gas at the inception of the plasma polymerization process. The bioactive agent-polymer composite-coated device is placed in a plasma chamber or other similar device and exposed to a monomer gas such as, for example, silicone-based monomers such as cyclic or acyclic siloxanes, silanes, silylimidazoles; fluorine-based monomers such as hydrofluorocarbons; aliphatic or aromatic hydrocarbons; acrylic monomers; N-vinyl pyrrolidone; ethylene oxide or combinations thereof. The monomer gas may have functional groups to allow covalent attachment of appropriate drugs by anchoring to these functional groups. Polymer blends, copolymers, or interpenetrating networks can be deposited in addition to homopolymer deposition, by simultaneous or subsequent introduction of two or more monomer gases. When introduced as a mixture, the ratio of the monomer gases could be adjusted to obtain desired properties. An energy source such as a radio frequency energy source is used to produce the low energy generating process.

Detail Description Paragraph:
[0045] As noted above, the release profile of the bioactive material from the

medical device is determined by many factors including the solubility of the bioactive agent in the barrier layer, porosity of both the composite and barrier layers, cross-linking density and thickness of the barrier layer, and hence resistance to the transport of the bioactive agent through the barrier layer.

Detail Description Paragraph:
[0046] FIG. 3 shows the effects of increasing the plasma polymerization time on the release rate of the bioactive agent. In FIG. 3, a siloxane barrier layer is applied onto a paclitaxel-polyurethane composite layer of a stent by a low energy plasma polymerization process including polyurethane and derivatives thereof including polycarbonate based, polyurea based, polyether based, and polyester based derivatives. Also included are Inter-Penetrating Network (INP)s such as siliconized polyurethane. The paclitaxel-polyurethane-coated stent is exposed to gaseous monomers of tetramethylcyclotetrasiloxane, which are then polymerized by low energy plasma polymerization onto the surface of the paclitaxel-polyurethane coating. As can be seen from FIG. 3, it is possible to achieve progressively slower release profiles of paclitaxel by increasing the plasma polymerization times, for example, from 6 seconds to 10 seconds to 20 seconds. An increase in polymerization time results in the formation of a thicker siloxane barrier layer, which in turn causes a sustaining effect on the paclitaxel release rate. Thus, the release profile of paclitaxel or other bioactive agent is precisely controlled by varying the time of the low energy plasma polymerization process.

Detail Description Paragraph:
[0047] Furthermore, modifications of any one or more of the basic plasma parameters such as the plasma polymerization time, the monomer flow rate, the pressure, and the energy applied offers the possibility of either changing the thickness and/or cross-linking density of the formed polymer. Both of these properties can, in turn, provide a means to control drug release by offering an enhanced resistance to the drug elution from the composite layer. Also, since the low energy plasma polymerization process utilizes gaseous phase for polymer application, coating selective areas on the coated stent may easily be achieved (by masking appropriate areas), which is difficult to achieve in a solution phase coating application.

Detail Description Paragraph:
[0048] In an alternative embodiment, a bioactive material(s) is incorporated into or on the outer surface of the barrier layer. For example, a second bioactive material is introduced into the barrier layer 20 by any suitable method. FIG. 4 shows a stent having an outer coating of bioactive agent, such as heparin, which is applied to barrier layer 20 to produce layer 25. The outer bioactive material, which may be the same or different from the bioactive agent of the bioactive agent-polymer composite layer, is placed in solution and applied to the barrier layer 20 by any suitable means, including dipping the coated medical device into the drug solution or by applying the solution onto the layer 20 such as by spraying. In the former method, the amount of bioactive material loading is controlled by regulating the time the barrier layer is exposed to the drug solution or dispersion, the extent of polymer cross-linking, the concentration of the drug in the solution or dispersion and/or the amount of barrier layer applied to the medical device.

Detail Description Paragraph:
[0051] In the event that the bioactive material of layer 5 is different from the bioactive material used with layer 20, the bioactive material in layer 20 provides a combination of biological effects achieved by either a synergistic or independent bioactivity of the two bioactive materials. For example, a combination of paclitaxel with corticosteroids or nitric oxide or nitric oxide donors as the bioactive material provides a synergistic effect. An example of a combination of bioactive agents that provide independent bioactivity useful for the treatment of restenosis is paclitaxel and heparin. In another example, heparin, heparin binding growth factors and nitric oxide donor are incorporated within the barrier layer 20 to obtain multiple benefits of non-thrombogenecity and enhanced endothelialization.

In an additional embodiment, layer 20 includes proteins or biological moieties to further modulate the drug release from layer 20.

Detail Description Paragraph:
[0052] When implanted, a substantial amount of the bioactive material contained in the bioactive agent-polymer composite layer 5 of the medical device is diffused into the affected area over an extended period of time and in a controlled manner.

CLAIMS:

1. An implantable medical device comprising: a structure adapted for introduction into a patient, wherein the structure comprises a base material; at least one composite layer comprising at least one bioactive agent and polymer material applied to at least a portion of the outer surface of said base material; and at least one barrier layer positioned over the composite layer, said barrier layer having a thickness adequate to provide controlled release of the at least one bioactive agent; wherein said barrier layer is formed in situ by a low energy plasma polymerization process of a monomer gas.

8. The device of claim 1, wherein the medical device is a device selected from the group consisting of a catheter, wire guide, cannula, stent graft, covered stent, vascular or other graft, cardiac pacemaker lead or lead tip; an angioplasty device or portion thereof; and any portion thereof.

13. A method for the localized delivery of a drug agent to a target location within a body, comprising the steps of: A) providing an implantable medical device which comprises a coated structure adapted for introduction into a patient, the structure comprising: (a) a base material; (b) at least one composite layer comprising at least one bioactive agent and a polymer material applied to at least a portion of the outer surface of said base material; B) forming at least one barrier layer comprising a polymer over the composite layer of said medical device, wherein said at least one barrier layer has a thickness adequate to provide a controlled release of the at least one bioactive agent, wherein said barrier layer is applied by a low energy plasma polymerization process which comprises: (i) placing said coated structure in a chamber; (ii) introducing at least one monomer gas into said chamber; and (iii) exposing the gas to a low energy source, whereby the monomer gas forms a barrier layer on the outer surface of the medical device; and C) delivering said implantable medical device to said target location.

Previous Doc Next Doc Go to Doc#

L11: Entry 54 of 75 File: USPT Sep 16, 2003

US-PAT-NO: 6620194
DOCUMENT-IDENTIFIER: US 6620194 B2

TITLE: Drug coating with topcoat

DATE-ISSUED: September 16, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ding; Ni	Plymouth	MN		
Helmus; Michael N.	Long Beach	CA		

US-CL-CURRENT: 623/1.43; 623/1.46

CLAIMS:

We claim:

1. A stent for implantation in a patient comprising a tubular body having open ends and a sidewall and a coating on at least a part of a surface of said sidewall, said coating further comprising an undercoat having an outer surface and comprising a polymeric material incorporating an amount of a biologically active material therein for timed delivery therefrom, and wherein said coating further comprises a topcoat comprising a polymeric material selected from the group consisting of fluorosilicone and polyethylene glycol (PEG), wherein said topcoat covers less than the entire outer surface of the undercoat and wherein said topcoat is substantially free of pores and porosigens.

2. The stent of claim 1 wherein the topcoat covers less than the entire undercoat while the device is implanted.

3. The stent of claim 1 wherein the topcoat covers less than the entire undercoat before the device is implanted.

4. The stent of claim 1 wherein the topcoat covers less than the entire undercoat before the device is implanted and while the device is implanted.

5. The stent of claim 1 wherein the polymeric material of the undercoat is a hydrophobic elastomeric material and wherein the polymeric material of the topcoat is a biostable, biocompatible material which provides long term non-thrombogenicity to the device portion during and after release of the biologically active material.

6. The stent of claim 1 wherein the topcoat reduces a burst release of the biologically active material as compared to a coated stent without the topcoat.

7. The stent of claim 1 wherein the stent is self-expandable and the sidewall comprises at least one opening therein and wherein the coating conforms to said sidewall in a manner that preserves said opening.

8. The stent of claim 1 wherein the biologically active material is heparin.

9. The stent of claim 1 wherein the topcoat covers from about 20% to 85% of the outer surface of the undercoat.

10. The stent of claim 1 wherein the topcoat has an average thickness of about 1 to 5 microns.

11. The stent of claim 1 wherein the topcoat has an average thickness of about the average particle size of the biologically active material.

Previous Doc Next Doc Go to Doc#

L11: Entry 55 of 75 File: USPT Jul 8, 2003

US-PAT-NO: 6589546
DOCUMENT-IDENTIFIER: US 6589546 B2

TITLE: Polymeric coatings for controlled delivery of active agents

DATE-ISSUED: July 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Kamath; Kalpana R.	Natick	MA		
Barry; James J.	Marlborough	MA		
Nott; Sepideh H.	Melrose	MA		

US-CL-CURRENT: 424/423; 424/422, 424/484, 424/486, 424/487, 424/488

CLAIMS:

What is claimed is:

1. An implantable medical device comprising: a structure adapted for introduction into a patient, wherein the structure comprises a base material; at least one layer comprised of at least one bioactive agent in a polymer matrix, applied to at least a portion of the outer surface of said base material; and at least one barrier layer positioned over the layer comprised of at least one bioactive agent in a polymer matrix, said barrier layer having a thickness adequate to provide controlled release of the at least one bioactive agent; wherein said barrier layer is formed in situ by a low energy plasma polymerization process.

2. The device of claim 1, further comprising a drug layer over said barrier layer wherein said drug layer includes heparin.

3. A method for the localized delivery of a drug agent to a target location within a body, comprising the steps of: A) providing an implantable medical device which comprises a coated structure adapted for introduction into a patient, the structure comprising: (a) a base material; (b) at least one layer comprised of at least one bioactive agent in a polymer matrix, applied to at least a portion of the outer surface of said base material; B) forming at least one barrier layer comprising a polymer over the layer comprised of at least one bioactive agent in a polymer matrix, wherein said at least one barrier layer has a thickness adequate to provide a controlled release of the at least one bioactive agent, wherein said barrier layer is applied by a low energy plasma polymerization process which comprises: (i) placing said coated structure in a chamber; (ii) introducing at least one monomer gas into said chamber; and (iii) exposing the gas to a low energy source, whereby the monomer gas forms a barrier layer on the outer surface of the medical device; C) introducing additional bioactive agent into said at least one barrier layer; and D) delivering said implantable medical device to said target

location.

4. The device of claim 1, wherein the barrier layer comprises a bioactive ingredient.

5. The device of claim 1, wherein said barrier layer is applied by a low energy plasma polymerization process which comprises: (i) placing said coated structure in a chamber; (ii) introducing at least one monomer gas into said chamber; and (iii) exposing the gas to a low energy source, whereby the monomer gas forms a barrier layer on the outer surface of the medical device.

6. The device of claim 1, wherein the base material comprises stainless steel or nitinol.

7. The device of claim 1, wherein the bioactive agent in the barrier layer ranges from 0.2 .mu.g/mm.sup.2 to 20 .mu./mm.sup.2.

8. The device of claim 1, wherein the bioactive agent in the barrier layer ranges from 1% to 50% w/w of the polymer matrix.

9. The device of claim 1, wherein the polymer matrix has a thickness in the range of about 5 to about 25 microns.

10. The device of claim 1, wherein the bioactive agent comprises paclitaxel and nitric oxide.

11. A method of making an implantable medical device comprising: A) providing an implantable medical device which comprises a coated structure adapted for introduction into a patient, the structure comprising: (a) a base material; (b) at least one layer comprised of at least one bioactive agent in a polymer matrix, applied to at least a portion of the outer surface of said base material; B) forming at least one barrier layer comprising a polymer over the layer comprised of at least one bioactive agent in a polymer matrix, wherein said at least one barrier layer has a thickness adequate to provide a controlled release of the at least one bioactive agent.

12. The method of claim 11, wherein said barrier layer is applied by a low energy plasma polymerization process which comprises: (i) placing said coated structure in a chamber; (ii) introducing at least one monomer gas into said chamber; and (iii) exposing the gas to a low energy source, whereby the monomer gas forms a barrier layer on the outer surface of the medical device.

13. The device of claim 12, wherein said monomer gas is selected from the group consisting of a cyclic or acyclic siloxane silicon-based monomers, silane silicon-based monomers, silylimidazoles silicon-based monomers, hydrofluorocarbon-based monomers; aliphatic or aromatic hydrocarbon-based monomer; acrylic monomer; and combinations thereof.

14. The implantable device of claim 11, wherein said polymer material comprises a polymer selected from the group consisting of polyurethane, polycarboxylic acids, polyorthoesters, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, proteins, polypeptides, silicones, polysaccharides, polyesters, polyacrylamides, polyethers, copolymers of vinyl monomers, and mixtures and copolymers thereof.

15. The device of claim 11, wherein said at least one bioactive agent is

paclitaxel.

16. The device of claim 11, wherein said at least one composite layer is formed by dissolution, dispersion, absorption, or adsorption of said at least one bioactive agent and polymer material.

17. The device of claim 11, wherein the thickness of said at least one barrier layer is less than 5000 .ANG..

18. The device of claim 17, wherein the thickness of said at least one barrier layer is about 50 to 2000 .ANG..

19. The device of claim 11, wherein the medical device is a device selected from the group consisting of a catheter, wire guide, cannula, stent graft, covered stent, vascular or other graft, cardiac pacemaker lead or lead tip; an angioplasty device or portion thereof; and any portion thereof.

20. The device of claim 11, wherein the base material of the structure comprises at least one of metal or polymer.

21. The device of claim 11, further comprising a drug layer over said barrier layer.

22. The device of claim 11, wherein said drug layer includes heparin.

23. An implantable medical device comprising: a structure adapted for introduction into a patient, wherein the structure comprises a base material; at least one layer comprised of at least one bioactive agent in a polymer matrix, applied to at least a portion of the outer surface of said base material; and at least one barrier layer positioned over the layer comprised of at least one bioactive agent in a polymer matrix, said barrier layer having a thickness adequate to provide controlled release of the at least one bioactive agent; wherein said barrier layer is formed in situ by a low energy plasma polymerization process of a monomer gas; wherein the at least one bioactive agent is paclitaxel; wherein the thickness of said at least one barrier layer is about 50 to 2000 .ANG.; wherein the bioactive agent in the barrier layer ranges from 0.2 .mu.g/mm.sup.2 to 20 .mu.g/mm.sup.2 .

Previous Doc Next Doc Go to Doc#

L11: Entry 67 of 75 File: USPT Mar 2, 1999

US-PAT-NO: 5876433
DOCUMENT-IDENTIFIER: US 5876433 A

TITLE: Stent and method of varying amounts of heparin coated thereon to control treatment

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lunn; Anthony C.	Princeton	NJ		

US-CL-CURRENT: 623/1.15; 606/198, 623/1.43

CLAIMS:

What is claimed is:

1. A stent for placement in a lumen of the body, and said stent placed into said lumen so as to contact said lumen, said stent coated with heparin wherein the stent is coated with enough heparin to insure above 0.7 pmol/cm.sup.2 antithrombin III is absorbed by the body when the lumen contacts said stent.

2. A stent according to claim 1 wherein the stent is coated with a plurality of layers of variable density of said heparin coating.

3. A method of placing the stent of claim 1 comprising the steps of:

determining the lesion site in said lumen to which the stent is to be employed;

predetermining the amount of heparin needed on a said stent at said lesion site in order to insure above 0.7 pmol/cm.sup.2 of antithrombin II is absorbed by the body with where the lesion contacts said stent;

coating said stent with the predetermined amount of said heparin; and

emplacing said stent into the body at said lesion site.

4. A stent of claim 1 wherein the stent is coated with enough heparin to insure the uptake of at least 10 pmol per cm.sup.2 of antithrombin III.

5. A method of placing a stent coated with heparin wherein the amount of heparin is variably adjusted depending on the desired use of the said stent comprising the steps of:

determining the lesion site to which the stent is to be employed;

predetermining the amount of heparin needed on a said stent at said lesion site;

coating said stent with the predetermined amount of said heparin wherein the stent is coated with enough heparin to insure at least 0.7 pmol/cm.sup.2 uptake of antithrombin III is absorbed by the body at said lesion site.

6. A method according to claim 5 wherein the stent is coated with a plurality of layers of variable density of said heparin coating.

7. A method according to claim 5 wherein the stent is useful for a particular lesion site in the body, said lesion site affecting the level of heparin coated on said stent.

8. A method according to claim 5 wherein the stent is coated with enough heparin to insure the uptake of at least 10 pmol per cm.sup.2 of antithrombin III.

Previous Doc Next Doc Go to Doc#

First Hit Previous Doc Next Doc Go to Doc#

End of Result Set

Generate Collection Print

L11: Entry 75 of 75 File: DWPI Jul 12, 2001

DERWENT-ACC-NO: 2001-475951
DERWENT-WEEK: 200239

TITLE: New implantable medical device coated with layers of a cationic polyelectrolyte carrier and at least one negatively charged therapeutic agent, useful as a stent, catheter, balloon catheter or combination of these.

INVENTOR: LEONG, K W; LI, W ; MAO, H

PRIORITY-DATA: 1999US-173743P (December 30, 1999), 2001US-0750779 (January 2, 2001)

Search Selected Search ALL Clear

PATENT-FAMILY:

	PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
☐	WO 200149338 A1	July 12, 2001	E	032	A61L029/16
☐	US 20020061326 A1	May 23, 2002		000	A61M037/00
☐	AU 200126232 A	July 16, 2001		000	A61L029/16

INT-CL (IPC): A61 L 29/16; A61 L 31/16; A61 M 37/00

ABSTRACTED-PUB-NO: US20020061326A
BASIC-ABSTRACT:

NOVELTY - A new implantable medical device coated with alternating layers of a negatively charged therapeutic agent and a cationic polyelectrolyte.

DETAILED DESCRIPTION - A new implantable medical device has a coating on at least one portion of at least one surface. The coating comprises an inner layer of a cationic polyelectrolyte carrier, a layer of at least one negatively charged therapeutic agent adsorbed onto the inner layer and optionally an additional layer or layers of both the cationic polyelectrolyte carrier and the negatively charged therapeutic agent, the additional layers alternating.

ACTIVITY - Cardiant.

A balloon catheter was coated with 40 layers of a DNA encoding human fibroblast growth factor-5 and was inserted into a blood vessel of a rat that perfuses the heart. Rats were sacrificed at 3 weeks following injection and capillary density was measured by computerized light microscopy. The results showed that a direct injection of a fibroblast growth factor-5 expression vector stimulates collateral vessel formation in areas of injected myocardium.

MECHANISM OF ACTION - None given.

USE - The medical device comprises a stent, a catheter, a balloon catheter or a combination of these. The device is useful for treating or reducing the occurrence or severity of a clinical disease or condition by delivering a therapeutic agent to a target location by implanting the device in or near the target location. The target location comprises at least one of brain, heart, liver, skeletal muscle, smooth muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostate, cartilage, bone, lung, blood vessel, ureter, urethra, urethra malignant growth or benign growth. Preferably the disease or condition is restenosis or angiogenesis and the therapeutic agents include rapamycin or is a malignancy or malignant cell growth and the therapeutic agents include paclitaxel.

ABSTRACTED-PUB-NO:

WO 200149338A
EQUIVALENT-ABSTRACTS:

NOVELTY - A new implantable medical device coated with alternating layers of a negatively charged therapeutic agent and a cationic polyelectrolyte.

DETAILED DESCRIPTION - A new implantable medical device has a coating on at least one portion of at least one surface. The coating comprises an inner layer of a cationic polyelectrolyte carrier, a layer of at least one negatively charged therapeutic agent adsorbed onto the inner layer and optionally an additional layer or layers of both the cationic polyelectrolyte carrier and the negatively charged therapeutic agent, the additional layers alternating.

ACTIVITY - Cardiant.

A balloon catheter was coated with 40 layers of a DNA encoding human fibroblast growth factor-5 and was inserted into a blood vessel of a rat that perfuses the heart. Rats were sacrificed at 3 weeks following injection and capillary density was measured by computerized light microscopy. The results showed that a direct injection of a fibroblast growth factor-5 expression vector stimulates collateral vessel formation in areas of injected myocardium.

MECHANISM OF ACTION - None given.

USE - The medical device comprises a stent, a catheter, a balloon catheter or a combination of these. The device is useful for treating or reducing the occurrence or severity of a clinical disease or condition by delivering a therapeutic agent to a target location by implanting the device in or near the target location. The target location comprises at least one of brain, heart, liver, skeletal muscle, smooth muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostate, cartilage, bone, lung, blood vessel, ureter, urethra, urethra malignant growth or benign growth. Preferably the disease or condition is restenosis or angiogenesis and the therapeutic agents include rapamycin or is a malignancy or malignant cell growth and the therapeutic agents include paclitaxel.

ABSTRACTED-PUB-NO: US20020061326A
EQUIVALENT-ABSTRACTS: NOVELTY - A new implantable medical device coated with alternating layers of a negatively charged therapeutic agent and a cationic polyelectrolyte. DETAILED DESCRIPTION - A new implantable medical device has a coating on at least one portion of at least one surface. The coating comprises an inner layer of a cationic polyelectrolyte carrier, a layer of at least one negatively charged therapeutic agent adsorbed onto the inner layer and optionally an additional layer or layers of both the cationic polyelectrolyte carrier and the

negatively charged therapeutic agent, the additional layers alternating. ACTIVITY - Cardiant. A balloon catheter was coated with 40 layers of a DNA encoding human fibroblast growth factor-5 and was inserted into a blood vessel of a rat that perfuses the heart. Rats were sacrificed at 3 weeks following injection and capillary density was measured by computerized light microscopy. The results showed that a direct injection of a fibroblast growth factor-5 expression vector stimulates collateral vessel formation in areas of injected myocardium. MECHANISM OF ACTION - None given. USE - The medical device comprises a stent, a catheter, a balloon catheter or a combination of these. The device is useful for treating or reducing the occurrence or severity of a clinical disease or condition by delivering a therapeutic agent to a target location by implanting the device in or near the target location. The target location comprises at least one of brain, heart, liver, skeletal muscle, smooth muscle, kidney, bladder, intestines, stomach, pancreas, ovary, prostate, cartilage, bone, lung, blood vessel, ureter, urethra, urethra malignant growth or benign growth. Preferably the disease or condition is restenosis or angiogenesis and the therapeutic agents include rapamycin or is a malignancy or malignant cell growth and the therapeutic agents include paclitaxel. WO 200149338A

CHOSEN-DRAWING: Dwg.0/5

Previous Doc Next Doc Go to Doc#

L10: Entry 8 of 42 File: PGPB Mar 11, 2004

PGPUB-DOCUMENT-NUMBER: 20040049265
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040049265 A1

TITLE: Drug coating with topcoat

PUBLICATION-DATE: March 11, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ding, Ni	Plymouth	MN	US	
Helmus, Michael N.	Long Beach	CA	US	

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
Schneider (USA) Inc.				02

APPL-NO: 10/ 603115 [PALM]
DATE FILED: June 24, 2003

RELATED-US-APPL-DATA:
Application 10/603115 is a continuation-of US application 09/942716, filed August 30, 2001, US Patent No. 6620194
Application 09/942716 is a continuation-of US application 09/573506, filed May 18, 2000, US Patent No. 6284305
Application 09/573506 is a division-of US application 08/996410, filed December 22, 1997, US Patent No. 6099562
Application 08/996410 is a continuation-in-part-of US application 08/663518, filed June 13, 1996, US Patent No. 6120536
Application 08/663518 is a continuation-in-part-of US application 08/526273, filed September 11, 1995, ABANDONED
Application 08/526273 is a continuation-in-part-of US application 08/424884, filed April 19, 1995, ABANDONED

INT-CL: [07] A61 F 2/06

US-CL-PUBLISHED: 623/001.42
US-CL-CURRENT: 623/1.42

REPRESENTATIVE-FIGURES: 9

ABSTRACT:

A coating and method for a coating an implantable device or prostheses are disclosed. The coating includes an undercoat of polymeric material containing an amount of biologically active material, particularly heparin, dispersed therein.

The coating further includes a topcoat which covers less than the entire surface of the undercoat and wherein the topcoat comprises a polymeric material substantially free of pores and porosigens. The polymeric material of the topcoat can be a biostable, biocompatible material which provides long term non-thrombogenicity to the device portion during and after release of the biologically active material.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a Continuation-In-Part of co-pending application Ser. No. 08/633,518, filed Jun. 13, 1996.

Previous Doc Next Doc Go to Doc#

L10: Entry 8 of 42 File: PGPB Mar 11, 2004

PGPUB-DOCUMENT-NUMBER: 20040049265
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20040049265 A1

TITLE: Drug coating with topcoat

PUBLICATION-DATE: March 11, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ding, Ni	Plymouth	MN	US	
Helmus, Michael N.	Long Beach	CA	US	

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	COUNTRY	TYPE CODE
Schneider (USA) Inc.				02

APPL-NO: 10/ 603115 [PALM]
DATE FILED: June 24, 2003

RELATED-US-APPL-DATA:
Application 10/603115 is a continuation-of US application 09/942716, filed August 30, 2001, US Patent No. 6620194
Application 09/942716 is a continuation-of US application 09/573506, filed May 18, 2000, US Patent No. 6284305
Application 09/573506 is a division-of US application 08/996410, filed December 22, 1997, US Patent No. 6099562
Application 08/996410 is a continuation-in-part-of US application 08/663518, filed June 13, 1996, US Patent No. 6120536
Application 08/663518 is a continuation-in-part-of US application 08/526273, filed September 11, 1995, ABANDONED
Application 08/526273 is a continuation-in-part-of US application 08/424884, filed April 19, 1995, ABANDONED

INT-CL: [07] A61 F 2/06

US-CL-PUBLISHED: 623/001.42
US-CL-CURRENT: 623/1.42

REPRESENTATIVE-FIGURES: 9

ABSTRACT:

A coating and method for a coating an implantable device or prostheses are disclosed. The coating includes an undercoat of polymeric material containing an amount of biologically active material, particularly heparin, dispersed therein.

The coating further includes a topcoat which covers less than the entire surface of the undercoat and wherein the topcoat comprises a polymeric material substantially free of pores and porosigens. The polymeric material of the topcoat can be a biostable, biocompatible material which provides long term non-thrombogenicity to the device portion during and after release of the biologically active material.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application is a Continuation-In-Part of co-pending application Ser. No. 08/633,518, filed Jun. 13, 1996.

Previous Doc Next Doc Go to Doc#

First Hit Fwd Refs Previous Doc Next Doc Go to Doc#

Generate Collection Print

L2: Entry 1 of 3 File: USPT Aug 19, 2003

US-PAT-NO: 6607598
DOCUMENT-IDENTIFIER: US 6607598 B2

TITLE: Device for protecting medical devices during a coating process

DATE-ISSUED: August 19, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schwarz; Marlene	Newton	MA		
Weber; Jan	Tuam			IE
Hansen; Henrik	Kinvar			IE
Lubinsky; Paul	Blackstone	MA		

US-CL-CURRENT: 118/500; 427/2.24, 427/2.25

CLAIMS:

What is claimed is:

1. A protective device for protecting a medical device during a coating process, comprising: an open-structure cage non-contactably surrounding a medical device, said cage having at least one contact point; a securement in contact with said at least one contact point and adapted to be in contact with the medical device.

2. The protective device of claim 1, wherein said cage is solvent-resistant.

3. The protective device of claim 1, wherein said securements are solvent-resistant.

4. The protective device of claim 1, wherein said cage has a plurality of contact points.

5. The protective device of claim 1, further comprising a plurality of securements in contact with said at least one contact point and adapted to be in contact with the medical device.

6. The protective device of claim 1, wherein said cage includes a ring wall.

7. The protective device of claim 1, wherein said cage includes a helical wall.

8. The protective device of claim 1, wherein said securement is integral to said contact point.

9. The protective device of claim 1, wherein said securement is attached to said contact point.

10. The protective device of claim 1, wherein said securement bears against said contact point.

11. The protective device of claim 1, wherein said securement is adapted to be attached to the medical device.

12. The protective device of claim 1, wherein said securement is adapted to bear against the medical device.

13. The protective device of claim 1, wherein said securement is constructed of metal.

14. The protective device of claim 1, wherein said securement is constructed of stainless steel.

15. The protective device of claim 1, wherein said securement is constructed of niconel.

16. The protective device of claim 1, wherein said securement is constructed of an inert polymer.

17. The protective device of claim 1, wherein said securement is constructed of teflon.

18. The protective device of claim 1, wherein said securement is coated with a solvent-resistant coating.

19. The protective device of claim 1, wherein said securement is coated with a solvent-inert coating.

Previous Doc Next Doc Go to Doc#

L3: Entry 1 of 2 File: USPT May 4, 2004

US-PAT-NO: 6730349
DOCUMENT-IDENTIFIER: US 6730349 B2

TITLE: Mechanical and acoustical suspension coating of medical implants

DATE-ISSUED: May 4, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Schwarz; Marlene C.	Auburndale	MA		
Tocker; Stanley	Wilmington	DE		

US-CL-CURRENT: 427/2.1; 427/2.24, 427/2.25, 427/2.26, 427/2.28, 427/2.3, 427/2.31, 427/240, 427/242, 427/295, 427/346, 427/348, 427/350, 427/372.2, 427/378, 427/407.1, 427/409, 427/424, 427/425, 427/591, 427/592, 427/600

CLAIMS:

What is claimed is:

1. A method of coating a medical device comprising: moving a medical device into a predetermined coating area; vibrating a conveyor below the medical device, the vibration of the conveyor forcing the medical device away from the vibrating conveyor, the conveyor urging the medical device from an entrance of the coating area to an exit of the coating area; and coating at least a portion of the medical device that has moved away from the vibrating conveyor.

2. The method of claim 1 wherein the medical device is periodically contacted by the vibrating conveyor such that the device first travels away from the vibrating conveyor and then travels back towards the vibrating conveyor until the medical device is contacted again by the vibrating conveyor.

3. The method of claim 1 further comprising: introducing a curing catalyst into the coating area.

4. The method of claim 1 wherein the coating contains a therapeutic.

5. The method of claim 1 wherein the medical device does not contact the vibrating conveyor.

6. The method of claim 1 further comprising: injecting a compressible fluid into the predetermined coating area.

7. The method of claim 1 further comprising: coating the medical device with a second coating.

8. The method of claim 1 further comprising: heating the medical device to a

temperature adequate to cure coating on the medical device.

9. The method of claim 1 further comprising: evacuating the predetermined coating area with a vacuum force.

10. The method of claim 1 further comprising: removing coating material from the predetermined coating area; and recycling the removed coating material.

11. The method of claim 1 wherein the medical device is selected from a stent, a medical balloon, a graft, a vena-cava filter or combinations thereof.

12. The method of claim 1 wherein a gas is used to position the medical device in the predetermined coating area and to remove the medical device from the predetermined coating area.

13. The method of claim 1 wherein the medical device is supported by a protective cage.

14. A method of coating a medical device comprising: moving a medical device into a predetermined coating area; vibrating a structure below the medical device, the vibration of the structure forcing the medical device away from the vibrating structure; and coating at least a portion of the medical device that has moved away from the vibrating structure, wherein the medical device does not contact the vibrating structure.

15. A method of coating a medical device comprising: moving a medical device into a predetermined coating area; vibrating a structure below the medical device, the vibration of the structure forcing the medical device away from the vibrating structure; and coating at least a portion of the medical device that has moved away from the vibrating structure, wherein the medical device is supported by a protective cage.

16. The method of claim 15 wherein the structure is an acoustic diaphragm.

17. A method of coating a medical device comprising: moving a medical device into a predetermined coating area; vibrating a structure below the medical device, the vibration of the structure forcing the medical device away from the vibrating structure; rotating the vibrating structure; and coating at least a portion of the medical device that has moved away from the vibrating structure.

Previous Doc Next Doc Go to Doc#